

REMARKS

Claim 1-12, 14, 18, 20, 21, 23, 26, and 38-47 are pending. Claims 14, 18, 23, 35 and 37 have been amended and claims 28-32 and 35-37 have been cancelled herein. No new matter has been added by way of the present amendment. For instance, claims 14 and 23 have been amended to clarify that the fused GFP is a substituted GFP of claims 1 and 18, respectively. Claim 18 has been amended to remove the language "at least." New claims 48 and 49 are supported by previously pending claim 36 as well as the present specification at page 2, lines 7-13 and page 7, lines 23-24. Lastly, new claim 50 is supported by originally filed claims 1, and 8-10. Accordingly, no new matter has been added.

In view of the following remarks Applicants respectfully request that the Examiner withdraw all rejections and allow the currently pending claims.

Objections to the Claims

The Examiner has objected to claim 35 pointing out that at line 5, the recitation of "chromophore is substituted with and amino acid" is incorrect. Applicants submit that claim 35 has been cancelled, thus, this objection is moot. Reconsideration and withdrawal thereof are respectfully requested.

The Examiner has also objected to claims 28-32 as being substantial duplicates of claims 3-7. Applicants respectfully traverse this objection and submit that claims 28-32 have been cancelled. Thus, this rejection is moot. Reconsideration and withdrawal thereof are respectfully requested.

Issues Under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 1-12, 14, 18, 20, 21, 23, 26, 28-33 and 35-47 under 35 U.S.C. §112, second paragraph for the reasons recited at pages 2 and 3 of the outstanding Office Action. Applicants respectfully traverse each of these rejections.

First, the Examiner asserts that the metes and bounds of what constitutes a "green fluorescent" protein cannot be determined. Applicants respectfully traverse.

Studying the GFP literature, even limited to GFPs isolated from *Aequorea victoria*, it is clear that every isolation thereof will be slightly different due to allelic differences among jelly fish. This is due to the fact that there are differences, small but significant, between the exact DNA and protein sequence between different individuals. In a literary sense, Applicants concede that the term "Green Fluorescent Protein" might not be the best choice; however, it is clear from the

references on record that this term is the term used in the scientific society. Reading, for example, the abstract of Heim (PNAS 1994), there is a discussion regarding "the availability of two visibly distinct colours of GFP, the green and the blue (Y66H)". Thus, the term GFP is not limited to the color green (which admittedly is contrary to intuition), and not to whether they have or can be substituted (Heim's blue GFP is Y66H substituted). Other colors of red, yellow and blue, in addition to green are known in the art as "Green Fluorescent Proteins"

Accordingly, Applicants submit that those skilled in the art are fully able to ascertain the metes and bounds of the term "green fluorescent" protein. This rejection should therefore be withdrawn.

Additionally, Applicants submit that the inclusion of claims 1-12 and 14 in this rejection is improper since these claims recite specific structures by way of reference to particular SEQ ID NOs. Thus, these claims should be allowable.

Second, the Examiner asserts that claims 14 and 23 are vague and indefinite for reciting "green fluorescent protein" because it is allegedly unclear if only the substituted GFP or both substituted and unsubstituted are encompassed. Applicants submit that claims 14 and 23 have been amended to clarify that the fused GFP is a substituted GFP of claims 1 and 18,

respectively. Thus, this rejection is moot. Reconsideration and withdrawal thereof are requested.

Issues Under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 18, 23, 35 and 36-47 under 35 U.S.C. §112, first paragraph for the reasons recited at pages 3-4 of the outstanding Office Action. Applicants respectfully traverse these rejections.

First, the Examiner asserts that claim 37 includes new matter for the recitation of "wild-type" GFP. Applicants disagree with the Examiner. A review of the specification and a particular figure provides a sufficient written description of "wild-type" GFP. For instance, wild-type GFP is disclosed in figure 2 as well as the present specification at page 9, lines 13-15). Regardless, claim 37 has been cancelled. Accordingly, this rejection is moot. Reconsideration and withdrawal thereof are requested.

Second, the Examiner asserts that the rejected claims relate to a genus of proteins which allegedly have an unlimited number of structural alterations in addition to having emission spectra outside of the spectra for the color green. Applicants traverse this rejection.

Applicants have attempted to clarify the scope of "green fluorescent protein", for instance, refer to the discussion above with respect to the Examiner's rejection under 35 U.S.C. § 112, second paragraph. It is true that the present claims will encompass fluorescent proteins which have emission spectra outside of the spectra for the color green. This, however, is explained by the fact that those of skill in the art refer to all variations of this class of protein as a "green fluorescent protein", regardless of whether the emission spectra is green, blue, red, yellow, or other.

Additionally, Applicants have clarified claim 18 to reflect that the fluorescent protein is substituted with "an amino acid" rather than "at least an amino acid." Thus, the rejected claims must have the specific substitutions and specific chromophores as recited. Accordingly, the claims do not encompass an unlimited number of structural alterations as asserted.

Additionally, Applicants draw the Examiner's attention to example 2 of the present specification. It is evident from comparing figure 6E with figure 6F that introduction of the F64L mutation into the blue GFP (Y66H-GFP) causes a marked increase in fluorescence when expressed at 30°C. This applies also to Mammalian cells (see example 3). It is stated that the

enhancing effect of GFP applies to both the blue GFP (Y66H-GFP) and to the red-shifted variant, S65T-GFP.

Accordingly, Applicants respectfully submit that the claims fully satisfy the requirements of 35 USC § 112, first paragraph. Reconsideration and withdrawal of these rejection are therefore requested.

Issues under 35 U.S.C. § 102(a)

The Examiner has rejected claims 18, 23, 35, 36-37, 40 and 43-47 under 35 U.S.C. § 102(a) as being anticipated by Ward et al., WO 95/21191 (hereinafter referred to as Ward '191). Applicants respectfully traverse this rejection.

Ward '191 fails to suggest or disclose the specific nucleic acid molecules currently claimed. The independent claims which are rejected over Ward '191 include claims 18 and 35. Claim 18 is distinct from Ward '191 and claim 35 has been cancelled. Accordingly, this rejection is moot. Reconsideration and withdrawal thereof are requested.

Issues under 35 U.S.C. § 102(b)

The Examiner has rejected claims 18, 23, 35, 37, 42, 43, 44, 45 and 47 under 35 U.S.C. § 102(b) as being anticipated by Zhang et al., Journal of Biological Chemistry, 1992, Vol. 267,

pp. 23759-23766 (hereinafter referred to as Zhang). Applicants respectfully traverse this rejection.

As a preliminary note, Applicants point out that the Examiner has incorrectly asserted that Zhang discloses a GluThrTryGlu sequence starting at position 306. A review of Zhang reveals that this sequence is actually GlyThrTryGly. Accordingly, Applicants will respond to this rejection based upon the above understanding that Zhang discloses the sequence of amino acids of GlyThrTryGly.

First, Zhang does not relate to a nucleic acid encoding a "green fluorescent protein." Rather, Zhang discloses a tyrosine phosphatase. This is an entirely distinct protein. Accordingly, based upon this distinction alone, no anticipation exists. As discussed above, the scope of the claims under 35 USC § 112, second paragraph or 35 USC § 112, first paragraph is no longer in question.

Second, the fact that Zhang discloses a 4mer of GlyThrTryGly amongst a totally different sequence is irrelevant. In fact, the fact that Zhang discloses some fluorescence data (see Fig 4 at p. 23763) does not alter this rationale and falls far short of a proper rejection for anticipation. Applicants recognize that in order for a reference to inherently anticipate a claim, it is not necessary that one skilled in the art would appreciate that the

prior art possesses the claimed characteristics. In this regard, it has been stated:

Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art. ... However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. *Atlas Powder Co. v. Hanex Products, Inc.*, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).

A theory of inherency must be supported by facts and/or technical reasoning that reasonably support a determination that the allegedly inherent characteristic necessarily flows from the teachings of the prior art. *Ex parte Levy* 17 USPQ2d 1461 (BPAI 1990) (emphasis added). In order for prior art to anticipate a claimed compound on the ground it is inherently produced in a prior art process, the inherency must be certain. *Glaxo, Inc. v. Novopharm Ltd.*, (EDNC 1993) 830 F. Supp 871, 29 USPQ2d 1126; *Ex parte Cyba* (POBA 1966) 155 USPQ 756; *Ex parte McQueen* (POBA 1958) 123 USPQ 37. The fact that a prior art article may inherently have the characteristics of the claimed product is not sufficient. *Ex parte Skinner* (BPAI 1986) 2 USPQ2d 1788. Inherency must be a necessary result and not merely a possible result. *In re Oelrich* (CCPA 1981) 666 F2d 578, 212 USPQ 323; *Ex parte Keith et al.* (POBA 1966) 154 USPQ 320.



Applicants submit that the disclosure of a sequence of GlyThrTryGly in a totally different protein, with no evidence that the ThrTryGly sequence is even a chromophore, and with no evidence that a tyrosine phosphatase is the same as a green fluorescent protein, is insufficient to shift the burden to applicants. Accordingly, no anticipation exists. Reconsideration and withdrawal of this rejection are requested.

The Examiner has also rejected claims 18, 23, 35, 37, 42, 43, 44, 45 and 47 under 35 U.S.C. § 102(b) as being anticipated by Mehra et al., Journal of Biological Chemistry, 1989, Vol. 264, pp. 19747-19753 (hereinafter referred to as Mehra). Applicants respectfully traverse this rejection.

Similar to Applicants traversal of Zhang above, Mehra is traversed for substantially the same reasons.

First, Mehra relates to a metallothionein II protein and not a green fluorescent protein. Second, Mehra does not disclose that the metallothionein II protein is fluorescent, but only luminescent. Accordingly, no anticipation exists. Reconsideration and withdrawal of this rejection are requested.

Issues Under 35 U.S.C. §102(e)

The Examiner has rejected claims 14 and 23 under 35 U.S.C. §102(e) as being anticipated by Chalfie et al., USP 5,491,084

(hereinafter referred to as Chalfie '084). Applicants respectfully traverse this rejection.

Applicants point out that claims 14 and 23 have been amended to clarify that the fused GFP is a substituted GFP of claims 1 and 18, respectively. Since Chalfie '084 fails to suggest or disclose the subject matter claimed, this rejection is moot. Reconsideration and withdrawal thereof are requested.

The Examiner has also rejected claims 14 and 18 under 35 U.S.C. §102(e) as being anticipated by Tsein et al., USP 5,625,048 (hereinafter referred to as Tsein '048). Applicants respectfully traverse this rejection.

Similar to that argued above with respect to Chalfie '084, Tsein '048 also fails to suggest or disclose the currently claimed nucleic acid molecule. Claims 14 and 23 have been amended to clarify that the fused GFP is a substituted GFP of claims 1 and 18, respectively. Thus, this rejection is moot. Reconsideration and withdrawal thereof are respectfully requested.

Issues under 35 U.S.C. § 103(a)

The Examiner has rejected claims 18, 35, 42, 43, 44 and 45 under 35 U.S.C. § 103(a) as being obvious over Marche et al. Biochemistry, 1976, Vol. 15, No. 26, pp. 5730-5737 (hereinafter

referred to as Marche) in view of what is well known in the art, as exemplified by Watson et al., The Molecular Biology of the Gene, 1987, Vol. I, page 437). Applicants respectfully traverse this rejection.

Marche fails to suggest or disclose a fluorescent protein, but rather uses fluorescent studies (actually circular dichroism spectra) to analyse the confirmation of the hormone Luliberin. The Examiner points out that Marche discloses a SerThrGly sequence with a preceding Gly residue. However, no motivation exists to utilize the sequence of Marche, relating to a Luliberin hormone, extrapolate the nucleotide sequence (even assisted by the teaching of Watson), and then add nucleic acids sufficient to make a green fluorescent protein. No *prima facie* case of obviousness exists. Applicants have already clarified that those of skill in the art understand the structure of a green fluorescent protein, however, there is very little motivation, if any at all, to modify a completely unrelated molecule, and thereby construct the presently claimed subject matter.

Reconsideration and withdrawal of this rejection are respectfully requested.

#### Provisional Obviousness-Type Double Patenting

The Examiner has provisionally rejected claims 1-3, 8, 9, 10, 11, 12, 18-21, 26 28 and 29 under the judicially created

doctrine of obviousness-type double patenting as being obvious over claims 10-15, 28-31 and 33 of copending application number 09/619,310. Applicants respectfully traverse this rejection. Applicants note that the scope of the claims has not being decided in either the present application or copending application serial number 09/619,310. As such, Applicants draw the Examiner's attention to MPEP §804 I-B wherein it is explained that if the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the Examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection, which has presumably been presented in the other application, into an actual double patenting rejection at the time the first application issues as a patent.

Initialed Form PTO-1449

Applicants thank the Examiner for the return of an initialed version of the Form PTO-1449, which accompanied the March 6, 2003 IDS.


If the Examiner has any questions or comments, please contact Craig A. McRobbie, Registration No. 42,874 at the offices of Birch, Stewart, Kolasch & Birch, LLP.

Application No: 09/872,364

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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